

NICKEL AND CERTAIN NICKEL COMPOUNDS

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CARCINOGENICITY

Nickel and certain nickel compounds are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity of nickel (CAS No. 7440-02-0) and the following nickel compounds in experimental animals: nickel acetate (373-02-4), nickel carbonate (3333-67-3), nickel carbonyl (13463-39-3), nickel hydroxide (12054-48-7 or 11113-74-9), nickelocene (1271-28-9), nickel oxide (1313-99-1), and nickel subsulfide (12035-72-2) (IARC V.2, 1973; IARC V.11, 1976; IARC S.4, 1982; IARC S.7, 1987). When injected intramuscularly, nickel induced incidences of fibrosarcomas in rats and hamsters of both sexes, local sarcomas in rats of both sexes, and local tumors with some metastases to pre-vertebral lymph nodes in female rats. When injected intrapleurally, nickel powder induced round cell and spindle cell tumors at the injection site in female rats. When administered by inhalation, nickel induced lymphosarcomas in female mice and anaplastic intraalveolar carcinomas, including one with extensive pulmonary adenomatosis, in male and female guinea pigs. Subdermal implantation of nickel pellets induced sarcomas surrounding the pellet in female and male rats. When injected intramedullarily into the femur, rats developed neoplasms at or near the site, including fibrosarcomas (neurogenic in origin), and one reticulum cell sarcoma with metastases. The same route of administration induced one metastasizing endothelial fibrosarcoma in a rabbit (IARC V.11, 1976; IARC V.2, 1973). When administered intraperitoneally, nickel acetate induced an excess of lung adenomas and carcinomas in mice (IARC S.4, 1982). When implanted intramuscularly, nickel carbonate induced sarcomas at the site of the implanted pellet. When administered nickel carbonyl through inhalation, male rats developed one pulmonary adenocarcinoma with metastases, extensive squamous metaplasms of the epithelium, neoplasms of the lung, one mixed adenocarcinoma and squamous cell carcinoma with metastases to the kidney and mediastinum, and papillary bronchiolar adenomas. Injection of nickel carbonyl into the tail vein of rats of both sexes induced malignant tumors including undifferentiated leukemia, pulmonary lymphomas, and individual incidences of liver, kidney, and mammary carcinomas. When millipore diffusion chambers containing nickel hydroxide were implanted in rats, local tumors were induced. When administered by intramuscular injection, nickelocene induced fibrosarcomas in rats and hamsters of both sexes. When administered by intramuscular injection, nickel oxide induced injection site sarcomas in mice and rats; administration by intramuscular implantation induced rhabdomyosarcomas and fibrosarcomas in mice and implantation site sarcomas in rats. When administered by intramuscular implantation, nickel subsulfide induced rhabdomyosarcomas and fibrosarcomas in mice and rats, rhabdomyosarcomas with distant metastases and implantation site sarcomas in rats, and tumors in mice. Palpable local tumors arose at implantation sites after nickel subsulfide pellets were removed from rats at various times. Intratracheal injection of nickel subsulfide induced malignant neoplasms of the lungs, adenocarcinomas, and squamous cell carcinomas, in rats of both sexes. Intramuscular injection of nickel subsulfide induced injection site sarcomas and rhabdomyosarcomas in rats and mice and fibrosarcomas and undifferentiated sarcomas in male rats; in addition, the sarcomas metastasized to distant sites, e.g., lungs, liver, heart, spleen, mediastinum, and mesentery and para-aortic lymph nodes (IARC V.2, 1973; IARC V.11, 1976). Nickel subsulfide induced malignant tumors in rats after insertion into heterotransplanted tracheas and after intrarenal, intratesticular, and intraocular administration (IARC S.4, 1982).

An IARC Working Group determined that there is limited evidence for the carcinogenicity of nickel and certain nickel compounds, and sufficient evidence for the carcinogenicity of nickel refining in humans (IARC S.4, 1982). A subsequent IARC Working

Group determined that there is sufficient evidence for the carcinogenicity of the group of nickel compounds in humans. However, the specific carcinogenic substance(s) could not be identified (IARC S.7, 1987). Several epidemiological studies demonstrated excess incidences of cancers of the nasal cavity, lung, and possibly the larynx in workers exposed to nickel or nickel compounds. The cancer hazards seemed to be associated with the early stage of nickel refining, and with exposure primarily to nickel subsulfide and nickel oxide (IARC V.2, 1973; IARC V.11, 1976; IARC S.4, 1982; IARC S.7, 1987).

PROPERTIES

Nickel occurs as silver metallic cubic crystals. It is soluble in dilute nitric acid, slightly soluble in hydrochloric acid and sulfuric acid, insoluble in cold and hot water and ammonia. It is available with a 99.9% purity and in grades which include electrolytic, ingot, pellets, shot, sponge, powder, high-purity strip, and single crystals. Nickel reacts violently with fluorine (F_2), ammonium nitrate, hydrazine, ammonia, a mixture of hydrogen (H_2) and dioxane, performic acid, phosphorus, selenium, sulfur, or a mixture of titanium and potassium chlorate. Nickel acetate occurs as a green powder that effloresces somewhat in air. It is soluble in acetic acid and water and insoluble in alcohol. It is available in a grade with purity > 99.0%. When heated to decomposition, nickel acetate emits irritating fumes. Nickel carbonate occurs as light green rhombic crystals or as a brown powder. It is soluble in dilute acids and ammonia and insoluble in hot water. Nickel carbonate is available with a 99.5% purity and occurs naturally as the mineral zaratorite. Nickel carbonate can react violently with iodine (I_2), hydrogen sulfide, or a mixture of barium oxide and air. Nickel carbonyl occurs as a colorless, volatile, inflammable liquid that has a musty odor. It is soluble in aqua regia, alcohol, ethanol, benzene, and nitric acid, slightly soluble in water, and insoluble in dilute acids and dilute alkalis. It is available in a technical grade. Nickel carbonyl explodes when exposed to heat or flame, and it can react violently with air, oxygen, bromine (Br_2), or a mixture of n-butane and oxygen. When heated or on contact with acid or acid fumes, nickel carbonyl emits toxic carbon monoxide fumes. Nickel hydroxide occurs as either green crystals or as an amorphous black powder. It is soluble in acid and ammonium hydroxide, but is practically insoluble in water. Nickel hydroxide is available in a grade containing about 60% nickel. Nickelocene occurs as dark green crystals. It is soluble in common organic solvents and insoluble in water. Nickelocene is a highly reactive compound which decomposes in air, acetone, alcohol, and ether. It is available as a grade containing 8 to 10% nickelocene in toluene. Nickel oxide is a green-black powder that becomes yellow when heated. It is soluble in acids and ammonium oxide and insoluble in both cold and hot water. It is available in a grade with 99% purity. Nickel subsulfide is a pale yellowish-bronze, metallic, lustrous solid. It is soluble in nitric acid and insoluble in cold and hot water. When heated to decomposition, nickel subsulfide emits toxic fumes of sulfur oxides (SO_x).

USE

In 1987, approximately 39% of the primary nickel consumed went into stainless and alloy steel production, 28% into nonferrous alloys, and 22% into electroplating. Ultimate end uses for nickel were: transportation, 24%; chemical industry, 15%; electrical equipment, 9%; construction, 9%; fabricated metal products, 8%; petroleum, 8%; household appliances, 7%; machinery, 7%; and other, 13% (USDOE, 1988). The many uses of nickel include use in alloys (e.g., low-alloy steels, stainless steel, dental fillings, copper and brass, permanent magnets, and electrical resistance alloys), electroplated protective coatings, electroformed coatings, alkaline storage batteries, fuel cell electrodes, and as a catalyst in the methanation of fuel gases and hydrogenation of vegetable oils. Nickel acetate is used as a catalyst and in the textiles industry.

as a mordant. Nickel carbonate is used in electroplating and in the preparation of nickel catalysts, ceramic colors, and glazes. Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and continuous nickel coatings on steel and other metals. It also has many small-scale applications, e.g., vapor seating of nickel and depositing of nickel in semiconductor manufacturing. Nickel hydroxide finds use in the manufacture of nickel salts. Nickelocene is used as a catalyst and complexing agent. Nickel oxide is used in nickel salts, porcelain painting, fuel cell electrodes, and the manufacture of stainless and alloy steel. There is no reported use for nickel subsulfide (Sax, 1987; IARC V.2, 1978; IARC V.11, 1976).

PRODUCTION

The United States produced an estimated 8 million lb of nickel from domestic ore in 1990 (USDOT, 1991). Ferronickel was produced by a smelter near Riddle, OR. Byproduct crude nickel sulfate was produced by four copper refineries, two firms that treated secondary copper, and scrap, nickel-base alloy scrap, and copper scrap. One firm converted particulate wastes from stainless steel plants and spent catalysts into nickel-bearing pigs for making stainless steel. Another company processed nickel hydroxide waste from several hundred metal finishers, and its product was shipped to a smelter for nickel recovery. The U.S. imported 320 million lb and exported 48 million lb (6 million lb; 42 million lb secondary nickel) in 1990 (USDOT, 1991). In 1989 the U.S. produced 764 thousand lb of nickel from domestic ore, and imported more than 278 million lb. Nickel exports exceeded 48 million lb (4.6 million lb primary nickel, 42.7 million lb secondary nickel) in 1989. More than 308 million lb of nickel were imported into the U.S. in 1988, and almost 42 million lb (5.4 million lb primary, nickel; 36.5 million lb secondary nickel) exported. In 1987, there was no domestic mine production of nickel. Generally, nickel is produced either as a by-product from copper refining or recycled or reclaimed from secondary sources. The 110 million lb of nickel produced in 1987 were from secondary sources. Imports of nickel were 302 million lb and exports were 2 million lb in 1987. In 1986, the production of nickel was by the following methods: > 2.3 million lb from mine production, 2.3 million lb from plant production of domestic ore, and 87.5 million lb from secondary sources. Imports of nickel in 1986 were 258 million lb and exports were 5.6 million lb. In 1985, mine production of nickel was 12.3 million lb, plant production from domestic ore was 10.5 million lb, plant production from foreign matte was 62.5 million lb, and secondary production was 107 million lb. Imports of nickel in 1985 were 315 million lb and exports were 45.5 million lb (USDOT, 1988). In 1985, 25.0 million lb of nickel powders were imported (USDOT Imports, 1986). In 1984, 29.1 million lb of nickel were produced by mine production, 19.2 million lb were produced by plant production from domestic ore, 70.7 million lb were produced by plant production from foreign matte, and 110 million lb were produced from secondary sources. In 1984, imports of nickel were 353 million lb and nickel powders were 30.1 million lb, and exports of nickel were 63.3 million lb (USDOT, 1988; USDOC Imports, 1985). In 1983, 66.8 million lb of nickel were produced by plant production from foreign matte and 100 million lb were produced from secondary sources. About 304.7 million lb of nickel were imported and 46.7 million lb were exported in 1983. Mine production of nickel was 6.4 million lb, plant production from domestic ore was 6.9 million lb, plant production from foreign matte was 83 million lb, and secondary production was 86 million lb in 1982. Also in 1982, 259.6 million lb of nickel were imported and 74.7 million lb were exported. In 1981, mine production of nickel was 24.2 million lb, plant production from domestic ore was 20.6 million lb, plant production from foreign matte was 77 million lb, and secondary source production was 104 million lb. In 1981, 418 million lb and 39.2 million lb of nickel were imported and exported, respectively. In 1980, 29.3 million lb of nickel were produced by mine production, 22.5 million lb by plant production from domestic ore, 66 million lb by plant production from foreign matte, and 98.6 million lb from secondary sources. In 1980, 378.3 million lb of nickel were imported and 38.9 million lb were exported

(USDOl, 1988; USDOl, 1985). The 1979 TSCA Inventory reported that in 1977, there were 21 companies producing 106.8 million lb of nickel and 30 companies importing 390.6 million lb (TSCA, 1979). In 1973, 36.6 million lb of nickel were produced from mine production (IARC V.11, 1976).

In 1985, 10.2 million lb of nickel compounds and 4.3 million lb of unspecified nickel compounds were imported, and 709,719 lb of unspecified nickel compounds were exported (USDOC Imports, 1986; USDOC Exports, 1986). Imports of nickel oxide in 1984 were 11.1 million lb and imports of unspecified nickel compounds were 195,840 lb (USDOC Imports, 1985). Also during 1984, exports of unspecified nickel compounds were 409,339 lb (USDOC Exports, 1985). The 1979 TSCA Inventory reported that in 1977, 15 companies produced 12.7 million lb and 2 companies imported 500 lb of nickel carbonate, with some site limitations; 13 manufacturers produced 781,000 lb of nickel hydroxide, with some site limitations; 27 companies produced 5.3 million lb and 12 companies imported 30.1 million lb of nickel oxide, with some site limitations; and 4 companies produced 121,200 lb of nickel subsulfide. The CBI Aggregate was less than 1 million lb for nickel carbonate and between 1 million and 100 million lb for nickel carbonyl and nickel subsulfide. Nickel acetate and nickelocene did not appear on the TSCA Inventory (TSCA, 1979).

EXPOSURE

The primary routes of potential human exposure to nickel and nickel compounds are ingestion, inhalation, and dermal contact. Possible exposures can occur because nickel is present in air, water, soil, food, and consumer products. NIOSH estimated that 250,000 workers in the United States were potentially exposed to nickel (including elemental nickel and inorganic nickel compounds) (NIOSHb, 1977a). OSHA estimated that 709,000 workers were possibly exposed to nickel and its compounds. Significant occupational exposure to nickel, through inhalation, at or near permissible levels may occur in a wide variety of occupations including battery makers, ceramic makers, electroplaters, enamelers, glass workers, jewelers, metal workers, nickel mine workers, refiners and smelters, paint-related workers, and welders. Inorganic nickel concentrations in workroom atmospheres usually range between 0.1 and 1 mg/m³. In addition, exposure may occur to the workforce from dermal contact with cutting oils contaminated with nickel and nickel-containing or nickel-plated tools (ATSDR, 1995g). The ACGIH has established threshold limit values (TLVs) as 8-hr time-weighted averages (TWAs) of 1 mg/m³ for nickel metal, 0.1 mg/m³ for soluble nickel compounds, as nickel, and 0.05 ppm and 0.35 mg/m³ for nickel carbonyl, as nickel (ACGIH, 1986).

The Toxic Chemical Release Inventory (EPA) listed 912 industrial facilities that produced, processed, or otherwise used nickel in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of nickel to the environment which were estimated to total 1.5 million lb. EPA estimated that nearly 720,000 people living within 12.5 miles of primary sources may possibly be exposed to nickel at concentrations up to 15.8 µg/m³ (median 0.2 µg/m³). As many as 160 million people live within 12.5 miles of all sources of nickel and nickel compounds, and they may possibly be exposed to median concentrations of 0.05 µg/m³. Ambient air concentrations of nickel in the United States are 6 ng/m³ in nonurban areas, and about 20 ng/m³ in urban areas, with higher values of up to 150 ng/m³ in large cities (New York City) and industrial areas (Merian, 1984). Also, the entire U.S. population may possibly be exposed to low levels of nickel (300-600 µg/day) in food and water. The following are typical concentrations of nickel found in various food categories: grains, vegetables, and fruits, 0.02-2.7 µg/g; meats, 0.06-0.4 µg/g; and seafoods, 0.02-20 µg/g. Cow's milk has been found to contain nickel concentrations of < 100 µg/L, and the typical

concentration of nickel in mother's milk ranges between 20 and 500 µg. Dietary nickel levels can increase because of food processing methods that leach nickel from nickel-containing alloys. Dietary intake of nickel has been estimated to range from 100 to 300 µg/day (ATSDR, 1995g). Nickel also is an essential micronutrient for plants; thus, eating plant material may be another potential source of exposure. There is a significant vector of exposure to the general population such as users of nickel-containing kitchen utensils and tableware (Sax, 1981). In the United States, nickel levels in drinking water are estimated to be less than 10 µg/L. Cigarette smoke is reported to contain up to 3 µg nickel/cigarette (OSH, 1982).

Environmental sources of nickel include emissions from coal- and oil-fired boilers, coke ovens, diesel-fuel burning, and gray-iron foundries. Total annual emissions from these types of sources was estimated to be 22.4 million lb. Crude oil contains on the average about 5 ppm nickel. In the United States, it was calculated that 60% of the atmospheric nickel emissions originate from oil-fired vessels. Soils normally contain 5-500 ppm nickel; soils from serpentine rock may contain as much as 5,000 ppm. The earth's crust and soils contain about 50 ppm of nickel, mostly in igneous rocks. Fresh and sea waters contain about 0.3 µg/L of nickel, ground water almost none. Urban effluents may contain 60 µg/L of nickel, of which 40% accumulate in sewage sludge. It has been determined that sewage sludges contain 20-1,000 ppm nickel with an average of 150 ppm. U.S. river basins contain 3-17 µg/L of nickel (Merian, 1984).

REGULATIONS

In 1980 CPSC preliminarily determined that nickel carbonyl was not present in consumer products under its jurisdiction. Subsequently, public comment was solicited to verify the accuracy of this information; no comments were received. Pending receipt of new information, CPSC plans no action on this chemical. EPA regulates nickel and nickel compounds under the Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), and Superfund Amendments and Reauthorization Act (SARA). Effluent guidelines have been established for nickel and nickel compounds under CWA. Reportable quantities (RQs) have been established for nickel, nickel carbonyl, and nickel hydroxide under CERCLA. RCRA regulates nickel and nickel compounds as hazardous wastes. RCRA and SARA subject nickel and nickel compounds to report/recordkeeping requirements. SARA also establishes threshold planning quantities. FDA has taken no action on nickel as a carcinogen because the data available are not adequate to assess its carcinogenicity through dietary exposure. Nickel is a compound generally recognized as safe (GRAS) when used as a direct human food ingredient. OSHA adopted permissible exposure limits (PELs) of 0.007 mg/m³ as an 8-hour TWA for nickel carbonyl and 1 mg/m³ as an 8-hour TWA for nickel metal and soluble nickel compounds; OSHA adopted these standards for toxic effects other than cancer. NIOSH recommended to OSHA that exposure to nickel be limited to 15 µg/m³ (10-hour TWA) because of observed carcinogenicity of nickel metal and all inorganic nickel compounds. OSHA regulates nickel and certain nickel compounds under the Hazard Communication Standard and as chemical hazards in laboratories. Regulations are summarized in Volume II, Table B-88.